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## **The role of binocularity in anisometropic amblyopia**

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## Abstract

Anisometropic amblyopia is unilateral by definition and current treatment recommendations reflect that characteristic. However, recent research suggests a binocular component that deserves consideration.

The aim of this review is to consider the levels of anisometropia deemed amblyogenic, and the cortical changes that occur in the presence of anisometropic amblyopia. Particular attention is given to cortical changes that impact the binocularity of these individuals.

Knowledge of binocular deficits in anisometropic amblyopia have implications for current, accepted treatment regimens which are monocular in nature. Therefore, the integrity of binocular function in anisometropic amblyopia and its impact on visual outcome will be evaluated. Given the rise in binocular treatments under clinical trial for amblyopia, this review also aims to evaluate the evidence of potentially enhanced benefits to anisometropic amblyopies from proposed new binocular therapies.

## Introduction

The use of the Greek word amblyopia (αμβλυωπία) can be traced back to approximately 480 BC when Hippocrates used the term to describe diminished acuity, including presbyopia, in otherwise apparently healthy eyes<sup>1</sup>. Current medical terminology advances the word amblyopia to define a unilateral or bilateral decrease in visual acuity, which continues after refractive correction or after the elimination of any pathological hindrance to vision (i.e. cataract) and in which no organic cause is usually found<sup>2,3</sup>.

Much of the current understanding of the etiology and mechanisms of amblyopia is informed by the revolutionary work of Hubel and Wiesel in the late 1950s and early 1960s. Hubel and Wiesel shed light on the structure of the visual cortex and identified the impact of early abnormal visual experience in animal cortices<sup>4</sup>. A key finding, and one that is used to support the theory of binocular therapy for amblyopia, is the shift in ocular dominance and almost complete loss of binocular function that occurs in cortical cells following a period of monocular occlusion<sup>5</sup>. They created the template for the study of neural plasticity<sup>6</sup>. Their work demonstrated that image disparity reduced neuronal representation in developing visual cortices<sup>7</sup>, therefore enabling the sub-classification of anisometropic amblyopia (unilateral amblyopia resultant from unequal refractive error). Their work also established a developmental period within which amblyopia could arise and be treated, which gave rise to the concepts of cortical plasticity and the critical and sensitive periods.<sup>8,9</sup>

Plasticity describes the brain's ability to rewire both structurally and functionally in response to external influences<sup>10</sup>. It results in the critical period – the time frame in which visual deprivation results in loss of function, and the sensitive period wherein visual improvement is possible with therapeutic intervention<sup>11</sup>. The critical period is thought to end by age 7-8 years old, whereas the sensitive period, once thought the same as the critical period, is now known to continue into the teenage years and possibly even early adulthood<sup>11</sup>. Plasticity alleviates the necessity of genetically encoding complex information required for cortical maturity<sup>6</sup>, but also leaves the visual cortex vulnerable to amblyopia.

The term binocularity applies to any visual function where both eyes contribute – it does not necessarily imply the interaction is a positive one. The existence of central suppression and inhibition has long been associated with amblyopia and refers to the hinderance of the amblyopic eye by the fellow eye at a cortical level<sup>12</sup>.

It is important to realize that binocular rivalry and suppression are normal functions of a healthy, balanced visual system: suppression in amblyopia activates similar mechanisms to those that aid normal binocular fusion when image disparity exceeds cortical tolerances<sup>13,14</sup>.

### Anisometropia

Anisometropia is the term given to a difference in spherical or cylindrical correction between the eyes<sup>8</sup>. The interocular difference deemed to be 'anisometropic' in scientific literature can be as little as 0.5 diopter sphere (DS) or diopter cylindrical (DC)<sup>15</sup>.

Anisometropia results in blurred vision particularly in one eye either part or all of the time<sup>7</sup> and may affect perceived contrast and size<sup>16</sup>.

### What level of anisometropia is amblyogenic?

The finding that anisometropia of greater than 1 DS increases the risk of amblyopia (2-14.5 years), but does not invariably cause it<sup>17,18</sup>, implies a protective factor against amblyopia that is not yet understood. There appears to be no fundamental difference between anisometropias where amblyopia is present or absent<sup>8</sup>.

Caputo et al.<sup>17</sup> analysed 119 pure anisometropic amblyopes aged 2-8 years (monofixation syndrome was ruled out in all participants) to investigate the minimum level of anisometropia that places an individual at risk of developing amblyopia. Although many subjects demonstrated a positive correlation between the degree of anisometropia and severity of amblyopia, there were enough outliers to prevent the authors from quantifying a lower limit for amblyogenic anisometropia. Weakley<sup>18</sup> reported similar results from a retrospective study of 411 anisometropic subjects (aged 3-14.5 years old). Although subjects with strabismus were excluded, those with a positive response for central suppression on the four prism diopter base out test were included. The groups with larger interocular differences reported the same prevalence of amblyopia and central suppression (presumably the same patients) but interestingly, in the groups with lower anisometropia (< 2 DS for both myopes and hypermetropes), the incidence of central suppression was higher than that of amblyopia. The high prevalence of monofixation syndrome in this cohort raises the question; could central suppression be the primary defect that has led to amblyopia and anisometropia rather than a result? However, it is generally accepted that amblyopia will develop at a faster rate than anisometropia<sup>8</sup> so amblyopia would still be expected to precede the development of clinically significant anisometropia.

The inclusion and definition of subjects with microtropia with identity or central suppression deserves consideration. A study analyzing 55 anisometropic amblyopes reported a 45% prevalence of microtropia (initial mean acuity in amblyopic eye was 20/80), the rest of their cohort demonstrated bifoveal fixation (initial mean acuity in amblyopic eye was 20/60). However, this finding did not appear to have any statistical significance with regards to the depth of amblyopia or recovery of visual acuity in the amblyopic eye<sup>19</sup>. Levi et al.<sup>16</sup> reported that the visual functions (acuity, contrast sensitivity and stereoacuity) of anisometropic amblyopes become more comparable to that of strabismic amblyopes as the hypermetropic anisometropia increases and compliments the finding of increased central suppression with increased hypermetropic anisometropia<sup>18</sup>.

Through animal studies, researchers have observed emmetropization – an active process by which eyes grow unequally to overcome low levels of induced anisometropia and achieve emmetropia<sup>8</sup>. As such, Caputo's 'outliers' who developed amblyopia in the presence of minimal anisometropia may have experienced a failure of emmetropization, or perhaps experienced a greater level of central suppression. The high correlation of amblyopia with central suppression in the Weakley study might suggest poor binocular functions are at the core of this susceptibility.

### Stages of visual development

Vision develops rapidly in the first six months of human life; there are anatomical<sup>20</sup> and physiological<sup>21</sup> changes that result in the subcortical driven visual responses of a newborn baby developing into the cortically determined visual responses of an adult. Since vision continues to develop postnatally, and in stages, it follows that the timing of

any visual impediment could result in quite different cortical consequences. For instance, in monkeys the magnocellular pathway is not affected during the late sensitive period (3-18 months) whereas the parvocellular pathway is<sup>22</sup>. The cortical changes that occur during the late sensitive period will be superimposed on changes that have occurred during the early sensitive period (0-3 months) if the visual insult occurs soon after birth<sup>22</sup>. Without knowing the age of onset, potentially combining differing amblyopia subtypes could mask findings that are characteristic of only one group.

Bilateral ametropic amblyopia is less severe than that seen in anisometropic amblyopia, suggesting that it is the dissimilarity between the two images rather than the associated blur that causes the pattern of visual dysfunction seen in these individuals<sup>16</sup>.

#### Development of anisometropic amblyopia – which comes first?

Clinically, anisometropic amblyopia is the finding of reduced visual acuity in the presence of anisometropia and the absence of pathology<sup>23</sup>. However, the concurrence of these diagnoses does not prove their chronology.

Three theories have been proposed to explain the association between amblyopia and anisometropia<sup>8</sup>.

- 1) Anisometropia causes amblyopia because of the persistent unocular blur it induces
- 2) Amblyopia causes anisometropia by way of disrupting the emmetropization process



- 3) There is a separate anomaly that causes cortical changes in visual function, which negatively impacts the emmetropisation process, and leads to amblyopia and anisometropia.

Anisometropia present during the first year of life usually resolves through emmetropization, whereas later onset anisometropia usually increases over time and follows the development of amblyopia<sup>24</sup>. The relative benignity of anisometropia in the first year is supported by the finding that most amblyopia diagnosed during the first year is associated with strabismus<sup>11</sup>. By three years of age, anisometropia and strabismus appear equally prevalent as the suggested etiology of a child's amblyopia and by age five anisometropia appears to be the cause of two thirds of amblyopia diagnosed in children<sup>13</sup>. This finding supports the second hypothesis that amblyopia precedes anisometropia by disrupting the emmetropisation process<sup>24</sup>, though the likelihood that strabismic amblyopia would present at any earlier age because of a manifest deviation is a confounding factor that should be considered.

Animal studies have found that inducing optical blur will precipitate the development of anisometropia and amblyopia<sup>8</sup>. There is an increased incidence of anisometropia in patients with ptosis<sup>25</sup>. Both these findings lend support to the third hypothesis.

A positive correlation has been reported between vision in the amblyopic eye and the level of fixation instability<sup>26,27</sup>. Of interest, one paper found a small but significantly greater level of fixation instability in the non-amblyopic eyes of children with anisometropia and/or strabismus when compared to normal controls<sup>26</sup>. The presence of this phenomenon in the absence of amblyopia could perhaps implicate it as an 'initial anomaly' and add further weight to the third hypothesis.

Aniseikonia is another phenomenon associated with anisometropia that deserves consideration. Aniseikonia can arise due to anisometropia, can be induced by optical correction or can arise from retinal or neurological asymmetry in the representation or configuration of the photoreceptors and their receptive fields<sup>28</sup>. This implicates aniseikonia in two respects; a retinal or neurological etiology would suggest aniseikonia as a cause of anisometropic amblyopia whereas optically induced aniseikonia (secondary to optical correction), may limit visual acuity and binocular function potential and therefore, treatment outcomes. Aniseikonia is known to increase the likelihood of suppression and be detrimental to stereoacuity<sup>28</sup>.

#### Primary visual cortex findings

The primary visual cortex (V1) is the earliest locus of functional and anatomical changes caused by anisometropic amblyopia and the neurons most significantly affected are those with binocular potential<sup>9,10,29</sup>. There is not only discussion about what mechanisms are responsible for the V1 changes in amblyopes but also the implications of these changes on extrastriate cortex. There is currently no test sensitive enough to distinguish between neural disarray and neuronal undersampling and, depending on how each term is defined, both could describe part of the same mechanism<sup>29</sup>. It appears that binocular connections in amblyopic individuals are actively suppressed rather than destroyed<sup>30</sup>. These findings argue against neuronal disarray, since normal binocular responses can be elicited in augmented conditions<sup>31</sup>.

#### Extrastriate findings – imaging studies

Farivar et al.<sup>32</sup> compared the multifocal functional magnetic resonance images (fMRIs) of 20 pure anisometropic amblyopes with ten controls and reported that amblyopic

visual cortices appeared more 'disordered' with reduced blood-oxygen-level dependent percentages and increased 'scatter' in the areas V1, V2 and V3. The deficits were greater in the extrastriate areas and correlated with the depth of amblyopia. This is likely a reflection of altered synaptic thresholds caused by long-term depression of the weak post-synaptic activity of the amblyopic eye<sup>31</sup>. However, there is still uncertainty as to whether the increased V2 deficit is merely a passive continuation of V1 deficits (the increase due to the higher number of binocular neurons) or an active amplification<sup>33</sup>.

Li et al.<sup>34</sup> found anomalous feedforward and feedback connections between the amblyopic eye and the ipsilateral hemisphere using fMRI in six amblyopes (three strabismic, one anisometropic and two with visual deprivation), indicating a possible cycle of anomalous visual information shared between the different cortical areas involved in visual processing. The authors suggested that the primary deficit causing these connectivity changes may originate in extrastriate areas. It was a small study, only one subject had central fixation and 20/100 vision in their amblyopic eye (the anisometrope) and individual results were not presented for comparison. The other five subjects had eccentric fixation or vision of 20/2000 Snellen acuity or worse in their amblyopic eye, making them a tenuous comparison for most anisometropic amblyopes.

Allen et al.<sup>35</sup> discovered changes in the white matter in all three thalamocortical tracts of their strabismic and anisometropic amblyopes when compared to their controls. No statistical inference could be determined based on the type of amblyopia due to the small number of participants.

Binocular rivalry vs. suppression in anisometropic amblyopia

There are differences between clinical suppression seen in amblyopia, and binocular rivalry suppression (BRS) seen in normal observers. BRS only occurs with dissimilar images<sup>36</sup> and with minimal inter-individual variability, whereas the magnitude of clinical suppression demonstrates large inter-subject fluctuations<sup>37</sup>. In the case of normal binocular vision, BRS is equally and mutually experienced by both eyes<sup>38</sup>, whereas in suppression associated with amblyopia there is significant asymmetry<sup>14</sup>.

The level of binocular rivalry and suppression can be altered in normal observers and to varying degrees by the manipulation of a uniocular image. There were four propositions about binocular rivalry made by Willem Levelt in 1965 that were 'updated' by JW Brascamp and colleagues<sup>36</sup>. They are as follows:

- 1) A stronger stimulus signal will increase the predominance of that eye's perception
- 2) Increasing the interocular difference between the stimuli will lengthen the average time of perceptual dominance of the stronger stimulus
- 3) Increasing the interocular difference between the stimuli will lead to a reduced perceptual alteration rate
- 4) Equally increasing stimulus strength to both eyes increases the perceptual alteration rate

By manipulating binocular rivalry some insight is gained as to what may occur in the amblyopic system. In normal subjects, tested within a laboratory setting, an adaptation is occurs whereby the disadvantaged eye (viewing an image with reduced luminance, contrast or other visual element) recovers and re-establishes a degree of dominance as dichoptic testing progresses<sup>36</sup>. Perhaps some anisometropes develop amblyopia in the

presence of mild anisometropia because they have a reduced ability to adapt or compensate for the inequality between the images.

The adaptation of the 'disadvantaged eye' to reassert dominance has been reported during treatment of anisometropic amblyopia: after monocular occlusion or penalization with a Bangerter foil, the penalized eye's binocular contribution will significantly increase for up to two hours after treatment<sup>39-41</sup>. The non-amblyopic eye's response to penalization, positively correlates with the success rate of amblyopia treatment<sup>40</sup>, but conversely has renewed interest in inverse occlusion therapy<sup>42</sup>, because the penalized eyes' response reveals the level of plasticity within the visual system.

#### Spatial frequencies and their impact on binocular rivalry

Elimination of high spatial frequencies by blurring an image has a greater impact on binocular rivalry than the filtering of low spatial frequencies<sup>43</sup>; one of an anisometropic amblyopes greatest deficits is in high spatial frequency detection<sup>16</sup>. Although the normal human cortex is most sensitive to spatial frequencies of 2-4 cycles per degree (cpd), a square wave stimulus containing the full range of spatial frequencies (2-15 cpd) will consistently achieve a stronger cortical response than any sinusoidal stimulus<sup>43</sup>. In normal observers, the eye with the higher contrast image dominates the binocular interaction<sup>43</sup>. The ability of the dominant eye to suppress the fellow eye increases exponentially with increased contrast, meaning there is not a single value that will rebalance the binocular image at all contrast levels<sup>38</sup>. As an etiological process, this would suggest the anisometropia precedes amblyopia, causing a variable reduction in the contrast of an image that the visual cortex cannot adapt to, particularly at high spatial frequencies, and ultimately leads to chronic suppression of that eye.

However, recent literature has consistently found a positive, direct correlation between the level of suppression and depth of amblyopia<sup>31,44-46</sup>. This supports an alternative hypothesis that suppression causes amblyopia and that abnormal binocular interaction is the primary etiology of amblyopia. Suppression caused by amblyopia would theoretically decrease with worsening amblyopia since poorer image quality requires a less active process to be ignored<sup>44,47</sup>.

A central question is whether amblyopic visual deficits are caused by active suppression, signal attenuation or both<sup>48</sup>. The ability of the adult brain to regain binocular function suggests active suppression rather than destruction of binocular connections<sup>48,49</sup>. The under representation of the amblyopic eye during binocular phase combination is more suggestive of signal attenuation<sup>48</sup> though some suggest that this is also a result of active suppression<sup>46</sup>. There are hugely differing views on the role of suppression, largely due to the different methods used to test and classify it<sup>50</sup>.

#### The effective contrast ratio

The increased interest in binocular therapy for amblyopia has directly affected how suppression is defined and tested. Many researchers now quantify suppression by measuring the effective contrast ratio (ECR) which determines the 'balance point'<sup>45</sup>. In very basic terms, this ratio is determined by presenting the amblyopic eye with an 100% contrast image; the contrast to the dominant eye is reduced until the images are perceived as equal<sup>31</sup>. The smaller the ratio, the greater the level of suppression<sup>45</sup>. This method has demonstrated that binocular interactions are still intact in individuals with central suppression<sup>51</sup> and that the suppression is not statistically different between groups of amblyopes with differing etiologies.<sup>37,44</sup>

The use of ECR to determine suppression raises interesting discussion points regarding suppression, including our description of the phenomenon. Kwon<sup>45</sup> found near normal ECRs in non-amblyopic strabismics (n=15, mean age 21.5 years, SD +/- 20.91 years), which would suggest little to no suppression; however clinical experience would determine this untrue. Perhaps suppression should be viewed as an encompassing description, reflecting any scenario of binocular input asymmetry. Suppression profiles may vary, explaining why two seemingly identical anisometropes have vastly different clinical presentations and visual outcomes. ECR documents an aspect of binocular function, but can be still highly asymmetric in fully recovered anisometropic amblyopes<sup>52</sup>, which undermines its validity as a measure of treatment success.

#### Visual functions and the presence of stereopsis in anisometropic amblyopia

A linear correlation between visual acuity and stereopsis has been reported<sup>18</sup>, especially when stereoblind anisometropes (with central fixation and no strabismus) were removed from analyses<sup>50</sup>. This is not a universal finding, however<sup>15,46</sup>. For anisometropic amblyopes, the absence of any demonstrable binocular function leads to an “extra deficit” that is disproportional to their reduction in grating and Vernier acuity. In a study of 495 participants (ages 8-40), pure anisometropes with no demonstrable central binocular function demonstrated similar defects to strabismic amblyopes in the absence of eccentric fixation or manifest strabismus<sup>53</sup>.

One great difficulty in reviewing literature on the topic of binocularity is what defines a positive binocular response; many studies rely on the Titmus fly to determine presence of stereopsis and it is widely accepted that this test is limited by multiple monocular clues<sup>54</sup>. One study differentiated their participants into binocular and non-binocular

groups based on a 1/9 score on Titmus circles and therefore applicability of their results, that binocularity was correlated to amblyopic monocular visual acuity, could be questioned<sup>55</sup>.

The differing tests for binocularity and interpretation of the results are not the only variables. There is a physiological difference between excitatory and inhibitory connections, i.e. two independent processes with differing susceptibility<sup>6</sup>. Stereopsis and binocular summation are regulated by excitatory connections and have been shown to be deficient or absent in pure anisometropic amblyopia<sup>18,46,50</sup>. Binocular rivalry and masking are controlled by inhibitory connections and these connections have demonstrated the same function and integrity in strabismic and anisometropic amblyopes when directly compared with normal observers<sup>51</sup>. Therefore, testing different visual functions could lead to paradoxical conclusions about the binocular state of an individual.

There is currently no fast, effective way to quantitatively define and record suppression in the clinical setting. The Worth Four Dot Test (W4DT) and Bagolini glasses are often used in clinical practice, but neither are quantitative<sup>12,46</sup>. The Sbisà bar allows for a more quantitative assessment of suppression, but the lack of scale and large variation in the interpretation of results undermines its clinical value<sup>56</sup>. The different binocular functions affected in amblyopia may appear significantly deficient (e.g. binocular summation) or intact (e.g. inhibitory connections). Thus, a positive 'suppression response' of the W4DT may indicate summation is abnormal, inhibition is intact, or both which does not illuminate the clinical evaluation.



It has been stated that suppression causes a binocular image to be perceived as monocular<sup>12</sup>, but absence of higher binocular functions does not equate to a monocular individual. Coarse stereopsis (involving large disparities) has been found intact in individuals with anisometropic amblyopia who demonstrate no fine stereopsis<sup>14,57</sup>.

### Extrastriate findings – behavioral studies

Abnormal spatial interactions noted when testing first order stimuli are believed to implicate either anomalous horizontal connections in V1 and/or abnormal feedback connections between V1 and V2<sup>58</sup>. An interesting series found a prevalence of 56% to 67% for perceptual visual defects (PVD) using dichoptic testing in children (n=82, mean age 6.33 years) and adults (n=24, mean age 27.13 years) with strabismic, anisometropic and microtropic amblyopia<sup>59,60</sup>. Although there was a correlation between both poorer visual acuity in the amblyopic eye and stereoacuity with the presence of PVD, it was not a consistent finding. Neuronal disarray may therefore be a finding in some amblyopic cortices but not all. The presence of PVD implicates the involvement of the extrastriate cortex, a finding supported by fMRI findings and behavioral studies. Physiologic tests of cortical neuron responses consistently found higher spatial resolution limits than those determined through behavioral studies<sup>24</sup>. There may therefore be a 'minimum requirement' for the number of cells producing the same response before it is demonstrated behaviorally<sup>29</sup>. It suggests either an undersampling of cortical neurons representing the amblyopic eye or that the deficits seen in V1 are further amplified in extrastriate cortex<sup>33</sup>. Flanking stimuli appear to improve visual functions in normal observers, whereas the same stimulus diminishes both an

anisometropic and strabismic amblyope's performance in either eye. This suggests a binocular cortical deficit involving at least V2<sup>58</sup>.

### Implications of extrastriate findings

The extrastriate cortex is exclusively binocular and all areas have shown abnormalities in the presence of amblyopia<sup>32</sup>. The involvement of the extrastriate cortex is also implicated by reports of abnormal visual function in amblyopic fellow eyes' spatial integration, contrast sensitivity and global motion perception<sup>61</sup>. This emphasizes both the binocular component of amblyopia and the range of visual deficits beyond acuity.

The ability of the fellow eye to match some of the deficits seen in the amblyopic eye could potentially reduce the density of suppression and protect the binocular potential of the visual system. Deficits in the fellow eye may extend the sensitive period by slowing the rate of maturity of the visual system and giving the amblyopic eye more time to recover<sup>61</sup>.

### Current treatment regimens and their limitations

Effective treatment of amblyopia is validated, in part, because the risk of binocular visual impairment doubles in individuals with amblyopia<sup>62</sup>.

The gold standard of treatment for amblyopia is patching<sup>46,50</sup>, and in more recent years penalization of the fellow eye with 1% atropine eye drops, which was shown by the Pediatric Eye Disease Investigator Group (PEDIG) to be an equally effective amblyopia treatment<sup>63</sup>. However, neither treatment plan offers 100% efficacy, with 15-50% of children unable to reach normal visual acuity levels<sup>13</sup>. There are several problems with patching, and to a lesser extent atropine. There is the time required to achieve a

significant result - 120 hours for one logMAR line improvement<sup>64</sup>, the social stigma often associated with a patch, boredom, and the somewhat underwhelming success rate<sup>13</sup>.

There is less social stigma attached to atropine therapy since a dilated pupil is less obvious than a patch but an increase in photosensitivity needs consideration especially during the summer months.

Regression is another problem facing the current treatment model. Weaning from high daily patch dosages (greater than six hours) to two hours daily before ceasing treatment completely has been shown to improve regression rate to about 15%<sup>65</sup>. Another study by the same group stated a regression rate of 19% but this was after a two year initial observation and treatment period<sup>66</sup>. Regression has, on several occasions, been found to reverse in the event of the fellow eye deterioration<sup>7</sup>, which suggests that a possible benefit is still gained from patching even when initial results are disappointing.

#### Treatment regimens to extend cortical plasticity

Research into drug therapy, such as levodopa, and noninvasive brain stimulation has been conducted in an effort to increase cortical plasticity and manipulate suppression<sup>67</sup>. However, in a randomised control trial of 139 children aged between 7 and 12 years with anisometropic, strabismic or mixed type (anisometropic and strabismic) amblyopia there was no statistically or clinically significant difference between those children given levodopa and patched and those given a placebo and patched<sup>68</sup>. Non-invasive brain stimulation has demonstrated that the visual functions in adult brains can be improved but the results are temporary; this area of research and the implications for cortical plasticity remain somewhat academic at this juncture<sup>69</sup>.

#### Binocular anisometropic amblyopia therapies

Binocular therapy rationalizes that binocular dysfunction is the primary cause of amblyopia. The primary goal is to normalize binocular functions, theorising that monocular visual acuity will improve secondary to the reduction of suppression and improvement in binocular functions<sup>13,31</sup>. Of note, patching has also demonstrated binocular improvements in functions such as stereopsis<sup>70</sup>.

Current literature supports the addressing of binocular deficits in amblyopia because the risk of residual amblyopia following treatment is 2.2 times greater in those individuals without demonstrable stereoacuity<sup>13</sup>. In addition, many children with normal or near normal visual acuity after treatment still demonstrate impaired binocular functions such as reduced stereoacuity at the conclusion of treatment<sup>10,15,71</sup>. When measuring suppression with the effective contrast ratio, suppression profiles of treated versus untreated amblyopes appear the same, demonstrating that significant deficits remain following successful traditional treatment<sup>44</sup>. This finding is also true of PVD which remained largely unchanged following occlusion therapy<sup>59</sup>.

There are three distinct methods of binocular therapy being tested in amblyopia treatment<sup>7</sup>

- 1) Anti-suppression techniques reduce the image contrast in the fellow eye to equal the perceived contrast of the amblyopic eye when viewing an image at 100% contrast. Some elements of the visual scene are shown only to the amblyopic eye, requiring both eyes to contribute equally to achieve an accurate perception of the image.
- 2) Balanced binocular viewing (BBV) blurs the image in the fellow eye to equal the acuity of the amblyopic eye.

- 3) Interactive binocular treatment (I-Bit) presents different aspects of a visual scene rapidly between each eye requiring accurate and constant binocular summation to see the presented image.

#### Research supporting binocular therapies

Numerous studies claim greater success with binocular therapies compared to conventional treatment; either a greater gain in visual function<sup>72,73</sup> or similar gains over a shorter time period<sup>74</sup>. Results from all studies discussed are presented in Table 1 for comparison.

Direct comparison between these studies is difficult because methods, protocols, length and type of treatment and follow up differ widely between them. The studies tend to be small ( $n = <40$ , and in most cases  $n <25$ )<sup>72-76</sup>, which diminishes the clinical application of their statistical analysis.

There is a wide age range both within and between these studies; some recruited only adults<sup>72</sup>, other cohorts were pediatric<sup>74,77</sup>, and some included adult and pediatric subjects<sup>75</sup>. Statistical analysis is therefore being applied or compared to a cohort of subjects that may be at different stages of visual maturity.

Participants' exposure to previous treatments varies widely between studies – subjects in one study were naïve to any treatment other than refractive adaptation<sup>74</sup>, another study only included subjects that were unsuccessful with conventional treatment<sup>75</sup> and one study included both unsuccessfully treated and previously untreated participants<sup>72</sup>. Many of the binocular treatments were performed in a laboratory which was not always replicated for the 'control' group<sup>72</sup>.

The short, or absent, follow up is another potential weakness in many of these studies<sup>72,73,76,77</sup>. The follow up cohort also tended to be much smaller than the number of participants in the main study which could underestimate the true level of regression associated with these therapies<sup>74</sup>.

Studies usually combined anisometropic and strabismic amblyopia for analysis, but two studies either separated their groups or only dealt with anisometropic amblyopia. They found very similar visual gains across their treatment and control groups.<sup>72,77</sup> One of these studies reported the best visual gains in the anisometropic controls (the movie group)<sup>72</sup>; the results from their entire cohort suggest a twofold gain in visual acuity using dichoptic video games vs monocular viewing of action movies.

The most dramatic results were a fourfold improvement in visual acuity and stereoacuity, and a four-factor reduction of suppression in patients treated with two weeks of dichoptic Tetris<sup>73</sup>. Identical results were reported for control group that were converted to binocular training after two weeks of monocular Tetris. The age of the adults participating, type of amblyopia and previous treatment were not disclosed, and such a finding has not been replicated on a large scale.

A study that recruited subjects who had not responded to conventional treatment reported a mean improvement of 0.34 logMAR through anti-suppression dichoptic training in 22 patients (ages 5 -73 years) with anisometropic or strabismic amblyopia<sup>75</sup>. The improvement seen in visual acuity is greater than reported by most studies. This may be, in part, the method of visual stimulation utilised during dichoptic training; random dot kinematograms where the subject had to identify the motion of the signal dots amongst the 'noise dots', rather than a game platform. Sessions lasted about two

hours in which time 1000 of these trials could be completed and is probably a more intensive form of visual stimulation when compared to dichoptic Tetris. The improvement correlated to the number to sessions completed but not age or severity of amblyopia. The acuity improvement was also maintained at a six month follow up after cessation of treatment.

The range of improvement reported in one study<sup>76</sup> (2-54%) highlights that wide range of visual improvements that can be seen within these small study groups. Although the average gain in visual acuity was 0.09 logMAR, only six out of fourteen subjects achieved an improvement of >0.1 logMAR.

As stated previously, the theory of binocular treatment is to primarily address the binocular dysfunction. However, it is the monocular acuity in the amblyopic eye that is presented as proof of the treatments' efficacy. Test results for binocular functions such as suppression are not as favorable even amongst studies supporting the use of these newer treatments. Two studies<sup>74,76</sup> reported no discernable difference in suppression levels post-treatment in their cohort. Though different methods of measurement between studies makes this finding difficult to interpret. A study reporting an improvement in stereopsis in six out of their seven anisometropes had recruited subjects that were naïve to all forms of treatment bar refractive adaptation, so this improvement may have also been witnessed after traditional treatment<sup>55,70</sup>.

High regression rates are another unsatisfactory aspect of traditional treatment where binocular therapies promise to deliver. A study with one of the longer follow up periods (six months) found the visual acuity gains were maintained and another study<sup>74</sup> reported a regression rate of 0.01 logMAR. However, the range of regression in this last study

was: a further gain of 0.15 logMAR to a regression of 0.23 logMAR (the average visual gain at the end of treatment was 0.27 +/- 0.22 logMAR) and only seven of the twenty-four original subjects were tested. There is simply not enough data from follow up visits to either support or reject this claim.

Binocular therapies demonstrate disappointing results when subjected to a randomized control trial (RCT). No statistical difference between visual gains made by the group playing dichoptic Tetris (n=56) and those playing a placebo version (n=59) in a patient population of seven years and older<sup>78</sup>. Another RCT<sup>79</sup> found slightly better visual gains in their patching group (n=186) compared to their group playing dichoptic Tetris (n=177), with no significant changes in stereoacuity or suppression for either group.

Both these RCTs utilized home based training and suggested this as a potential cause for the failure to replicate some of the visual gains seen in lab-based studies of dichoptic training. There were also compliance and boredom factors. However, any effective amblyopia treatment must be home based in order to be practical, and the compliance problems represent what clinicians will likely face if this becomes an accepted alternative treatment. Although some lab-based results are very promising<sup>75</sup> they must be replicable on a large scale if their clinical applicability to amblyopia treatment is valid.

A more recent RCT<sup>80</sup> tested a newer binocular game ("Dig Rush"), thought to be "more engaging", to address some of the compliance issues reported in previous RCTs. At the conclusion of eight weeks, >75% adherence to treatment was reported by 75% treatment group, though log data from their devices recorded an adherence rate of 56%. Their results found a 1.7 logMAR improvement in their control group, who continued with full-time spectacle correction (n=69), compared to a 1.3 logMAR improvement in



the test group receiving binocular therapy (n=69). Their conclusion supported previous RCTs that there was no benefit to binocular therapy.

Another RCT<sup>81</sup> reported significant visual gains of approximately three letters (0.07 logMAR) after only 3 hours of treatment (n=50) yet identical results were reported in their control group (n=25), perhaps revealing a practice effect only. The 'shutter glasses' used in the control group were suggested as a cause. Regardless, the success of their control group undermines the power of 'binocular therapy' in this series.

A meta-analysis of 26 studies reporting statistically significant visual gains in adult amblyopes (n=243) concluded that, on average, these subjects experienced a 0.17 logMAR gain in visual acuity. However, the studies analyzed had used dichoptic training, perceptual learning, video games or occlusion in their treatment. The only significant factor found was initial visual acuity; the poorer the initial visual acuity, the more likely a genuine visual improvement (beyond test/retest variability) would occur. Initial visual acuity also determined the stereoacuity outcome; the better the initial visual acuity (and stereoacuity) the higher likelihood an improvement in stereoacuity would be noted. Type of treatment, monocular versus binocular, had no impact on visual outcomes<sup>82</sup>.

## Conclusion

The cortical deficits and response to treatment reported in anisometropic amblyopia are not consistent. However, the presence of binocular functions appears to be a key determinant of these outcomes. Patching is a monocular therapy, yet it can affect binocular improvements such as stereopsis. Conversely, binocular therapies often improve monocular visual acuity, but do not always improve binocularity and patients

with 'resolved' amblyopia (equal visual acuity) may still demonstrate abnormal visual functions.

Anisometropia, suppression, amblyopia and failure to emmetropize may result from a cortical primary deficit in binocularity and currently there is insufficient evidence to determine the chronological order of these events. The possibility of multiple anisometropic etiologies could be linked to treatment success. The emerging connection between some measures of suppression density reduction and amblyopia treatment response is a promising field for further investigation. Suppression may be an appropriate description to reflect a spectrum of binocular input asymmetries.

Both monocular and binocular therapies boast great success, however determining which eyes will respond to amblyopia treatment, needs further research. A spectrum of visual functions are affected by amblyopia, thus a spectrum of treatments may be necessary to repair the damage.

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